

A Bradford Hill Appraisal of Raised Visceral Adipose Tissue causing Coronary Heart Disease:

Introduction

Excess adiposity is heterogeneous. While subcutaneous fat is largely inert metabolically, **visceral adipose tissue (VAT)**—the ectopic depot within the abdominal cavity and around the heart and great vessels—exhibits intense endocrine and immune activity. VAT secretes pro-inflammatory cytokines, adipokines, and lipid mediators; drains (in part) to the portal circulation; and is closely linked to insulin resistance, dyslipidaemia, endothelial dysfunction, and atherogenesis. The clinical question is whether **raised VAT is a cause of coronary heart disease (CHD)** rather than merely a correlate of overall adiposity.

Applying **Bradford Hill's nine aspects of association**—strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy—helps structure this causal appraisal(1,2)

1) Strength of Association

A causal claim is easier to sustain when associations are strong. Large imaging-based cohorts and pooled analyses show that **higher VAT (by CT/MRI or surrogates such as the Visceral Adiposity Index)** associates with increased incident cardiovascular events, including myocardial infarction and cardiovascular death, independent of BMI and traditional risks. Observational estimates commonly report **20–60 % higher event rates** across ascending VAT strata after multivariable adjustment.(3–6)

For example, a 2024 pooled analysis reported that individuals in the highest **Visceral Adiposity Index (VAI)** categories had higher risks of **CHD and cardiovascular mortality** versus those in the lowest categories (7). In older adults, greater VAT was associated with a **~60 % higher risk of stroke or MI** after adjustment(4,5). The strength is moderate rather than extreme (relative risks often < 2) but notably **persists after accounting for BMI**, suggesting VAT conveys risk beyond general adiposity.(3,4,8).

Caveats. Magnitudes vary by measurement method (imaging vs indices), sex, ethnicity, and age. Some single-centre studies show attenuation after aggressive risk adjustment, and VAI—though practical—is an **indirect** proxy for VAT, potentially introducing misclassification.

2) Consistency

The VAT–CHD association is **replicated across datasets, geographies, and designs**: community cohorts using CT/MRI quantification; clinic-based series; and studies of **epicardial adipose tissue (EAT)**—the heart’s visceral fat depot—assessed by echocardiography, CT, or MRI. Reviews in *Nature Reviews Cardiology* and *Circulation: Cardiovascular Imaging* synthesise multiple cohorts in which higher EAT tracks with **coronary plaque burden, stenosis, and events**(9–13).

Similarly, umbrella reviews conclude that **visceral**, more than subcutaneous, adiposity aligns with adverse cardiometabolic profiles and cardiovascular outcomes, with consistent directionality across populations (3,11).

3) Specificity

Specificity is weaker in modern epidemiology: a single exposure rarely causes a single disease. VAT is **multisystemic**—linked not only to CHD but also to **stroke, heart failure, arrhythmia, non-alcoholic fatty liver disease, and type 2 diabetes**. However, **cardiovascular complications—especially coronary atherosclerosis—are the signature harms** observed for intra-abdominal VAT and for cardiac visceral fat (EAT or pericoronary adipose tissue). (7,9–11,14). In other words, while not exclusive to CHD, VAT’s most clinically salient expression is cardiovascular and coronary.

4) Temporality

Exposure must precede outcome. Prospective cohorts measuring VAT (CT/MRI) at baseline demonstrate **subsequent** increases in incident CHD or major adverse cardiovascular events over years of follow-up(4–6). Additionally, **Mendelian randomisation (MR)**—using germline variants that predispose to higher VAT mass—supports temporal ordering: **genetically instrumented VAT** is associated with elevated risks of **CAD, MI, and heart failure**, implying exposure (VAT tendency) predates disease.(4,8,15)

5) Biological Gradient (Dose–Response)

Numerous studies report **graded risk** with ascending VAT tertiles or quartiles. Indices such as VAI show **linearly increasing hazards** for CHD and cardiovascular death across categories(6). Observational imaging cohorts demonstrate that **more VAT (or higher EAT**

volume/thickness) tracks with **greater plaque burden**, higher prevalence of vulnerable plaque features, and higher event rates.(11,14)

MR findings also suggest a **dose–response**: genetic instruments associated with **larger increments in VAT mass** correspond to **larger increases in CAD risk**, consistent with a gradient not easily explained by confounding.(4,8,15)

Caveats. The gradient may flatten at extremes; variability in VAT measurement (single-slice CT vs volumetric MRI or EAT thickness) can blur dose–response precision.

6) Plausibility (Mechanistic Explanation)

Mechanistic evidence is compelling. VAT is characterised by:

- A **pro-inflammatory secretome** (IL-6, TNF- α , MCP-1), adipokines, and excess free fatty acids promoting endothelial dysfunction and oxidative stress.(3)
 - The **portal hypothesis**, whereby VAT lipolysis delivers FFAs and cytokines directly to the liver, driving hepatic insulin resistance, VLDL overproduction, and atherogenic dyslipidaemia.((3)
 - **Paracrine signalling from EAT**, where the absence of a fascial barrier allows local transfer of inflammatory mediators to the coronary adventitia, plausibly accelerating plaque progression and instability.(5,9)
 - These pathways are summarised in authoritative reviews linking VAT and EAT to impaired coronary vasomotion, microvascular dysfunction, and vulnerable plaque phenotypes.(5,6,9,16)
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7) Coherence

Findings from pathology, imaging, physiology, genetics, and epidemiology are mutually reinforcing. Autopsy and imaging studies demonstrate lipid-rich epicardial and pericoronary fat adjacent to culprit plaques, while CT and MRI show correlations between VAT/EAT burden, coronary calcium, non-calcified plaque, and adverse outcomes(9,16).

Importantly, VAT remains associated with **residual cardiovascular risk** even after LDL lowering and blood-pressure control, supporting an independent pathobiology rather than simple confounding.(3)

8) Experiment (Intervention)

Although no randomised trials target VAT reduction alone, converging interventional evidence supports causality:

- **Bariatric and metabolic surgery**, which preferentially reduces visceral fat, is associated with substantial reductions in major cardiovascular events and mortality in large meta-analyses (event reductions ~25–58 %; mortality ~35–40 %)(11,15,17).
- **Pharmacological therapies** that reduce VAT (e.g. GLP-1 receptor agonists) lead to regression of EAT and improvements in vascular and metabolic markers.(5,16)
- **Mendelian randomisation** acts as a natural experiment, demonstrating that genetically determined VAT excess causally increases coronary risk.(4,14)

Together, these lines of evidence satisfy Bradford Hill's experimental criterion.

While an ideal RCT isolating VAT from other weight-loss effects is unlikely, the **triangulation** of surgical, pharmacologic, imaging, and genetic evidence is persuasive for causality.

9) Analogy

Analogous ectopic fat depots (e.g. **hepatic steatosis**, **perivascular adipose tissue**) are implicated in **atherogenesis** and **vascular dysfunction**. EAT—the heart's visceral fat—demonstrates local paracrine toxicity to the coronary wall, mirroring VAT's systemic effects(9,11,14,16). By analogy, **more ectopic or visceral fat → more coronary risk** is a consistent pattern across depots and studies.

Synthesis and Counterpoints

Raised VAT satisfies **most** of Bradford Hill's aspects with **moderate-to-strong** support:

- **Strength / Consistency** across cohorts and methods.
- **Temporality** via prospective imaging and MR.
- **Gradient** across VAT strata.
- **Plausibility / Coherence** from rich mechanistic literature.
- **Experiment** via bariatric surgery outcomes and converging MR evidence.
- **Analogy** through EAT and other ectopic fat depots.

Limitations include measurement heterogeneity, residual confounding, and difficulty isolating VAT's effect from concurrent improvements in glycaemia, blood pressure, and inflammation. Nevertheless, the **totality of evidence** supports the conclusion that **raised VAT is a causal driver of CHD risk**, not merely a bystander or surrogate for BMI.

Limitations of VAT Measurement

Despite strong causal evidence, measurement of visceral adipose tissue (VAT) in clinical practice has important limitations. **Indirect surrogates** such as body mass index, waist circumference, waist–hip ratio, and composite indices (e.g. Visceral Adiposity Index) incompletely capture true visceral fat burden and may misclassify risk, particularly in individuals with normal BMI but high ectopic fat. Imaging-based quantification using CT or MRI provides the most accurate assessment of VAT volume and distribution, but cost, radiation exposure (for CT), and limited availability constrain widespread use.(5,9,16). Single-slice CT methods and echocardiographic measures of epicardial adipose tissue, while practical, may underestimate total visceral fat and introduce inter-observer variability. Furthermore, VAT is **dynamic** and responsive to diet, physical activity, sleep, and pharmacotherapy; static, single-time-point measurements may therefore fail to reflect cumulative exposure or recent change. Finally, sex-, age-, and ethnicity-specific thresholds for pathological VAT remain incompletely standardised, limiting uniform clinical cut-offs and risk stratification.(3,8).

Conclusion

Using Bradford Hill's framework, **raised visceral adiposity** meets key tenets of causality for **coronary heart disease**. The association is consistent, temporally ordered, graded, biologically plausible, coherent across disciplines, supported by quasi-experimental genetics and by interventions that preferentially reduce visceral fat and lower cardiovascular risk. Remaining uncertainties relate more to quantifying effect size than to the existence of a causal link. Clinically, this justifies **VAT-targeted risk assessment and management**—for example, waist-to-height ratio screening, selective VAT imaging, and treatment programmes that prioritise VAT loss through diet, resistance and HIIT training, sleep optimisation, and—when indicated—pharmacological or surgical strategies.

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